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## Catalytic High Pressure Synthesis of Hindered $\beta$ -Aminoesters.

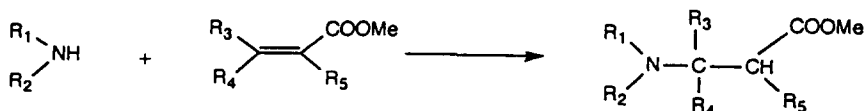
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**Abstract :** Hindered  $\beta$ -aminoesters are obtained in fair to high yields by the conjugate addition of amines to  $\alpha,\beta$ -unsaturated esters, both substrates harbouring bulky groups, under high pressure in the presence of catalytic amounts of ytterbium triflate.

$\beta$ -Lactams are widely used *inter alia* as antibiotics.<sup>1</sup> A simple potential route involves in a first step the conjugate addition of primary amines to  $\alpha,\beta$ -ethylenic esters yielding  $\beta$ -aminoesters which can be subsequently converted into  $\beta$ -lactams by known procedures.<sup>2,3</sup> However, the limits of the method are rapidly reached as the reaction is extremely sensitive to steric hindrance.<sup>4,5</sup> In fact, only acrylic esters and simple unsubstituted primary amines enter smooth addition under moderate temperature conditions.<sup>6</sup> Two notable improvements in the field were recently reported : the use of appropriate catalysts such as lanthanide triflates<sup>7</sup> and high pressure.<sup>8</sup> Ytterbium triflate was shown to be an effective catalyst in the addition of ethyl crotonate to benzylamine<sup>7</sup> whereas crotonates were reacted with chiral amines under 5-15 kb pressure to yield enantioselectively  $\beta$ -aminoesters.<sup>8</sup>

Our laboratory has initiated a kinetic study in order to quantify the pressure effect in a series of reactions involving amines and  $\alpha,\beta$ -ethylenic esters of increasing bulkiness.<sup>9</sup> Remarkably, it could be observed that the reactions were very sensitive to pressure and characterized by high negative values for the volume of activation ( $-50$  to  $-60$  cm<sup>3</sup>.mol<sup>-1</sup>), meaning acceleration factors of about  $2 \cdot 10^4$  to  $1.5 \cdot 10^5$  at 10 kb and 25  C. Quite obviously, such significant increases in reaction rates make pressure as a parameter of choice for the synthesis of sterically congested  $\beta$ -aminoesters. In addition, we felt that the combination of physical (high pressure) and chemical (catalysis) activation could emerge as an exceptional powerful synthetic method in the preparation of hindered  $\beta$ -aminoesters which, otherwise, could not be synthesized by traditional procedures.

**Table 1. :** Effect of catalyst<sup>a</sup> :

Catalyst	Yields (%)			
	A <sup>b</sup>	B <sup>b</sup>	C <sup>b</sup>	D <sup>b</sup>
none	26 (8)	62	1.5	30
Eu(fod) <sub>3</sub>	-	59	1.5	29
Yb(OTf) <sub>3</sub>	100 (42)	95	8	63
ZrCl <sub>4</sub>	-	100	6	88
LiClO <sub>4</sub> <sup>c</sup>	-	34	-	-
LiClO <sub>4</sub>	-	14	-	-
Bu <sub>4</sub> NF	-	-	traces	-
PBu <sub>3</sub>	-	52	-	19
DABCO	-	-	0	0

<sup>a</sup> (5 % in moles), solvent (acetonitrile), t (24 h), amine:ester (2:1)

<sup>b</sup> Reaction A (PhCH<sub>2</sub>NH<sub>2</sub> + ethyl crotonate, 1 bar, 30° C) (in parentheses, yields obtained under conditions of ref. 7 : 20° C, solvent (CH<sub>2</sub>Cl<sub>2</sub>), t (15 h)

Reaction B (iPrNH<sub>2</sub> + methyl crotonate, 1 bar, 30° C)

Reaction C (iPrNH<sub>2</sub> + methyl methacrylate, 1 bar, 30° C)

Reaction D (tBuNH<sub>2</sub> + methyl crotonate, 3 kbar, 36° C)

<sup>c</sup> 5M in diethyl ether. No acetonitrile was added

In a first stage, the results of ref. 7 are checked under two different conditions (Table 1). At 20° C, 1 bar, 15 h in CH<sub>2</sub>Cl<sub>2</sub>, the yield of ester is 8 % (0 % according to ref. 7) and 42 % (vs 92 % in ref. 7) without and in the presence of the ytterbium catalyst respectively. In CH<sub>3</sub>CN, a temperature increase of 10° C raises these values to 26 % and 100 % respectively, indicating a relatively facile reaction compared to the reactions studied below (Table 2). Then, we screen some catalysts including strong and mild Lewis acids as well as organic bases.<sup>10</sup> Clearly, organic bases are not suitable. The strong Lewis acid ZrCl<sub>4</sub> is a potent catalyst, however, the results are puzzling as ZrCl<sub>4</sub> can undergo complexation with amines and act as polymerization catalyst (for example in reactions involving methyl acrylate). LiClO<sub>4</sub> in diethyl ether is much less efficient. Among the two lanthanide compounds, only ytterbium triflate improves the yield, in harmony with the former study<sup>7</sup> though not to the same extent. Accordingly, the high pressure experiments are carried out in the presence of Yb(OTf)<sub>3</sub>. The results are listed in Table 2.

**Table 2.** : High pressure synthesis of  $\beta$ -aminoesters<sup>a</sup> :

Entry	Methyl ester	Amine	T (°C)	P(bar)	Yield (%) <sup>b</sup>	
					no catalyst	with Yb(OTf) <sub>3</sub>
1	acrylate	iPr <sub>2</sub> NH	50	1	0	17
			50	3000	13	80
2	methacrylate	tBuNH <sub>2</sub>	30	1	0	4
			30	3000	11	47
3	methacrylate	Ph <sub>2</sub> CHNH <sub>2</sub>	50	1	0	0
			50	3000	0	--
			50	9500	34	100
4	methacrylate	iPr(Me)NH	50	1	0	10
			50	3000	28	50
5	crotonate	iPr(Me)NH	50	1	2	6
			50	3000	55	61
6	crotonate	iBu <sub>2</sub> NH	50	1	0	7
			50	3000	20	47
7	crotonate	iPr <sub>2</sub> NH	50	1	0	0
			50	3000	0	0
			50	9500	0	10
8	DMA <sup>c</sup>	iPrNH <sub>2</sub>	50	1	0	0
			50	3000	1	7
			50	9500	45	78
9	DMA <sup>c</sup>	tBuNH <sub>2</sub>	50	1	0	0
			50	3000	0	0
			50	9500	5	13

<sup>a</sup> Solvent (acetonitrile), 24 h, catalyst (5 % mole).

<sup>b</sup> Isolated yields.

<sup>c</sup> 3,3-dimethyl acrylate.

At atmospheric pressure, no or very little reaction takes place in the absence of the ytterbium compound. Carrying out the reactions with Yb(OTf)<sub>3</sub> as the catalyst leads to low yields of aminoester, except in entry 1 where a 17 % yield is observed. Increasing the pressure promotes the formation of  $\beta$ -aminoesters. Combination of pressure and lanthanide catalysis is particularly efficient in most cases. The presence of the catalyst increases the yield by a factor varying between 1.1 and 7, indicating a catalyst effect depending on the substrates involved. An interesting result is provided by entry 7 showing a 10 % yield of the corresponding aminoester vs 0 % without catalyst. The reaction with diisobutylamine (entry 6) occurs easier, since the product is formed at lower pressure in substantial yield. However, it is clear that high pressure is the determining parameter (compare the yields in the uncatalyzed vs catalyzed reactions when pressure is increased from atmospheric to 3 kb).

In the last years, it was shown that some reactions, including Michael additions,<sup>11</sup> could be promoted in water.<sup>12</sup> In order to compare pressure and hydrophobic effects, the experiments listed in entries 1 and 4

(atmospheric pressure) are carried out in water.<sup>13</sup> No reaction is observed at all even, surprisingly, when the water soluble Yb(OTf)<sub>3</sub>-catalyst is added.

In conclusion, pressure associated with catalysis by ytterbium triflate<sup>14</sup> is a remarkable tool in the synthesis of hindered  $\beta$ -aminoesters which may give access to interesting crowded biological systems as the bioactivity is dependent not only on their chemical, but also structural (steric) properties.<sup>15</sup> In addition, the present syntheses demonstrate the uniqueness of the pressure procedure versus novel activation methods such as use of water or LiClO<sub>4</sub>-diethyl ether<sup>16</sup> as reaction medium which are unable to lead to the hindered structures described here. The present results stay in agreement with earlier reports on the beneficial effect of pressure on the synthesis of crowded molecules.<sup>17</sup>

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## References and Notes :

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